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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,451	07/31/2001	Louis Schofield	18862	8055

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/830,451	SCHOFIELD ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 79-137* is/are pending in the application.

4a) Of the above claim(s) *4-8,17, 79,80,89-99, 101,107,111-115,121-123 and 126-137* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124, 125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/11/08 has been entered.

Applicant's response filed 9/11/08 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I (claims 1-18 and 79-125), and species election of inducing an immune response, upregulation of the Th2 response, treatment or prophylaxis of the disease condition malaria using a GPI with the sequence EtN-P-[Mα2]Mα2Mα6Mα4Gα6Ino-Y in Applicant's response filed 10/17/03.

Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 are presently being examined.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3, 9-16, 18, 103-106, 108-110, 116-120, 124 and 125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims were rejected on the basis set forth below in the prior Office Action of record.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir.1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed method of activating CD1-restricted Th cells (including CD1+ NK1.1+ T cells, Th2 cells), said method comprising administration of a complex comprising GPI, including for treatment or prophylaxis via administration of a GPI complex.

The instant claims encompass use of a complex of GPI that comprises a molecule other than a protein or peptide antigen to activate or induce Th cells *in vitro* or *in vivo*, including for treatment or prophylaxis.

The specification discloses that GPIs consist of a conserved core glycan (Manα1-2Manα1-6Manα1-4GlcNH$_2$ linked to the 6 position of the myo-inositol ring of PI (sentence spanning pages 1 and 2). The specification further discloses other GPI that do not appear to comprise the conserved core glycan as defined above (pages 3-7), for example, EtN-P-Manα2-Manα6-M-Y (page 4 at line 2) or Manα2-Manα6-M-Y (page 7 at line 1). The specification discloses that "GPI complex" is a reference to a GPI moiety coupled to any other molecule, and said molecule may be any molecule for which an immune response is sought, for example, a carbohydrate or a peptide or protein (page 20 at lines 29-31).

The specification as filed does not provide written description support for any molecule in complex with GPI except for an antigenic peptide or protein or carbohydrate. Adequate written description requires more than a mere statement that it is part of the invention and along with a recitation of a function such as inducing Th cells. The derivative or equivalent itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

In addition, a definition by function does not suffice to define the genus because it is only an indication of what the property the complex has, and if one extends the analysis in the instant case, what the complex does (*i.e.,* it induces a CD1-restricted Th cell response), rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many such species may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. One of ordinary skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

Applicant's arguments in the amendment filed 9/11/08 have been fully considered, but are not persuasive.

Applicant's position is of record on pages 2-3, briefly that the GPI molecule comprises a core glycan, the specification describes that a GPI molecule can be further substituted with sugars, phosphates and ethanolamine groups and GPI fatty acid moieties can also be substituted or modified (page 2 of specification at the first paragraph), so the specification has adequately described a representative number of species within the genus of GPI complex.

The paragraph spanning pages 1-2 of the instant specification discloses that GPIs are ubiquitous among eukaryotes, that they consist of a conserved core glycan Manα1-2Manα1-6Manα1-4GlcNH$_2$ linked to the 6 position of the myo-inositol ring of PI, and that these GPIs are built up on the cytoplasmic face of the endoplasmic reticulum by the sequential addition of sugar residues to PI by the action of glycosytransferases, then are transported across the membrane to the luminal side of the ER, and exported to the cell surface, free or in covalent association with proteins. The terasaccharide core glycan maybe further substituted with sugars, phosphates and ethanolamine groups in a species and tissue-specific manner. That is, the specification describes the manufacture and export of naturally occurring GPIs in eukaryotes. The specification further discloses that GPI fatty acid moieties can be either diacylglycerols, akyulacylglycerols, monoalkylglycerols or ceramides, with additional palmitoylations or myristoylations to the inositol ring, *i.e.,* again those that are naturally produced by eukaryotes.

The specification discloses that "GPI complex" is a reference to a GPI moiety coupled to any other molecule, and said molecule may be any molecule for which an immune response is sought, for example, a carbohydrate or a peptide or protein (page 20 at lines 29-31); however, the other molecule does not have to be a molecule for which an immune response is sought, including to a carbohydrate a peptide or protein antigen, and thus the "GPI complex" may comprise undisclosed other molecules from the universe of "molecules."

For these reasons and the reasons of record, it is the Examiner's position that the instant specification has not provided written description for the claimed method of activating Th cells comprising administering a GPI complex, including for the treatment and/or prophylaxis of a mammalian disease condition, and including those conditions recited in the instant claims.

5. Applicant's arguments in the response filed 9/11/08 have overcome the rejection of claims 1-3, 9-16, 18, 103-106, 108-110, 116-120, 124 and 125 in the prior Office Action of record under 35 U.S.C. 112, first paragraph. With regard to claims 1-3, 9-16 and 18, Applicant's argument is deemed persuasive. With regard to the remaining claims that recite "prophylaxis," the Examiner notes that the instant specification on page 45 at lines 1-5 redefines "prophylaxis" thus: ""Similarly, "prophylaxis" does not necessarily mean that the subject will not eventually contract a disease condition. Accordingly, treatment and prophylaxis include amelioration of the symptoms of a particular condition or preventing or otherwise reducing the risk of a particular condition. The term "prophylaxis" may be considered as reducing the severity of onset of a particular condition."

The Examiner notes that the prior rejection of record did not require clinical data in order that the enablement requirement be met. No *in vivo* data of any kind is disclosed in the instant specification, and the evidentiary reference establishes unpredictability in the art of prevention of malaria, whether in an animal model or in a human, and hence unpredictability in extrapolating the ability of GPIs in activating NK-T cells with prevention of malaria or any other disease or condition.

6. For the purpose of prior art rejections, the filing date of the instant claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 is deemed to be the filing date of the PCT application PCT/AU99/00929, *i.e.,* 10/27/99, as the foreign priority application AU PP 6758 does not support the claimed limitations of the instant application. There is no disclosure of the chemical species recited in the said instant claims in the said foreign priority application.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3, 9-16, 18, 81-88, 100 and 102 stand rejected under 35 U.S.C. 102(b) as being anticipated by Schofield *et al* (J. Exp. Med. 1/93 177: 145-153, of record) as evidenced by Nagata *et al* (Eur. J. Immunol. 1993 23: 1193-1196, of record), Gerold *et al* (Mol. Biochem. Parasit. 1996 75: 131-143, of record), Gerold *et al* (J. Biol. Chem. 1994 269(4): 2597-2606, of record), Berhe *et al* (Mol. Biochem. Parasit. 1999 103: 273-278, of record), Schofield *et al* (Science 283: 225-229, 1/8/99, of record), Joyce *et al* (Science 1998 279: 1541-1543, IDS reference) and Sieling *et al* (Science 1995 269: 227-230, IDS reference).

Schofield *et al* teach a strong correlation between TNF and IL-1 levels in sera of malarious individuals and the severity of the disease, wherein plasma TNF levels were twice as high in surviving cerebral malaria patients as in those with uncomplicated malaria, and those that died of the cerebral malarial disease had ten times elevated levels. Schofield *et al* teach that administration *in vivo* of specific neutralizing antibodies against TNF affords some protection to mice infected with lethal malaria. Schofield *et al* teach that excess production of TNF in response to the malarial parasite contributes to the severe pathology and death in both rodent and human infections. Schofield *et al* teach administration *in vivo* in mice of P. *falciparum* or T. *brucei* GPI or analogues that also comprise diacylglycerol and phosphatidylcholine. Schofield *et al* teach that several major antigens of the malaria parasite are covalently linked to GPI, including the MSP-1 and MSP-2 antigens on the merozoite surface, currently under consideration as vaccine candidates. Schofield *et al* teach that immunization of mice with highly purified malaria GPI prepared from mature P. *falciparum* MSP-2 leads to a serological anti-GPI response with T independent features, and the anti-GPI sera are able even at high titration to neutralize TNF induction and lipogenesis by both the heterologous MSP-1 antigen and whole parasite extracts, *i.e.,* anti-GPI administered for treatment of induced malarial disease *in vivo* in mice. Schofield *et al* teach providing clinical protection against malarial disease, either by passive transfer of neutralizing anti-GPI antibodies or by immunization against the GPI or various non-toxic analogues for *in vivo* production of anti-GPI antibodies (especially page 152, page 149, page 150). Schofield *et al* teach cerebral malaria is a type of malaria to be treated by administering GPI (see entire article, especially introduction on pages 145-146, page 146 at the third full paragraph, results and discussion, page 152 at column 2).

Evidentiary reference Nagata *et al* teach that Th2 cells secrete IL-4, IL-5 and IL-6 and provide the major help for antibody production of T cells (especially first paragraph on page 1193).

Evidentiary reference Gerold *et al* (1996, of record) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane, the GPI anchors having the Mα2Mα2Mα6Mα4-GlcInositol phosphate linked to diacyl glycerol, a lipid. Gerold *et al* (1996) also teach that the core glycans of both protein-GPI anchors possess the same structure as the potential GPI-anchor precursor $Pf_{g1}\alpha$ taught by the evidentiary reference Gerold *et al* (1994) cited below (see entire article).

Evidentiary reference Gerold *et al* (1994, of record) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane. Gerold *et al* (1994) teach that MSP-1 and MSP-2 possess GPI anchors with the same neutral glycan as $Pf_{g1}\alpha$. Gerold *et al* (1994) teach that they are supposed to have the structure ethanolamine-phosphate-Mα2Mα2Mα6Mα4GlcN-PI based upon identical fragmentation products to the *T. brucei* GPI-anchor precursor P2, and the said structure further comprises a lipid (see entire article).

Evidentiary reference Berhe *et al* (of record) teach GPIs from different isolates of *Plasmodium falciparum,* including the isolate taught by the art reference Schofeld *et al* (1993), have a set of GPIs structurally identical to the GPIs described for the reference parasite line FCBR, and the core structure is ethanolamine-phosphate-Mα2Mα2Mα6Mα4-glucosamine-acyl-phosphatidylinositol or ethanolamine-phosphate-Mα2Mα6Mα4-glucosamine-acyl-phosphatidylinositol, and wherein the GPIs have ester linked fatty acids at the C-terminal end (see entire article).

Evidentiary reference Schofield *et al* (1999, of record) teach that the GPI anchors in *Plasmodium falciparum* comprise the structure ethanolamine-phosphate-Mα2Mα2Mα6Mα4-GlcNα6-myoinositol phosphate-diacyl glycerol (see entire reference, especially Figure 1A). Schofield *et al* (1999) further teach that the proliferative and IL-4 (*i.e.,* Th2 cytokine) response to PfGPI of NK 1.1+/CD4+ T cells is independent of MHC and can be blocked by an anti-CD1 mAb, indicating CD1 restriction.

Evidentiary reference Joyce *et al* (of record) teach that CD1d binds GPI through its phosphatidylinositol aspect with high affinity. Joyce *et al* further teach that CD1d controls the function of NK1+ T cells that play an immunoregulatory role in responses to foreign and self antigens.

Evidentiary reference Sieling *et al* (of record) teach GPI-CD1-mediated stimulation of T cell subsets, the GPI from mycobacterial species possessing a phosphatidylinositol aspect similar to the GPI taught by the other evidentiary references cited herein.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. When a claim recites using an old composition or structure (*e.g.,* GPI or analogues) and the use is directed to a result or property of that composition or structure (activating $CD4^+$ $NK1.1^+$ Th2 cells following administration of GPI) then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. v. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. v IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Applicant's arguments in the amendment filed 9/11/08 have been fully considered, but are not persuasive.

Applicant's position is of record on pages 19-20, briefly that: the Schofield *et al* reference teaches protocols that are different from the claimed method, *i.e.,* Scholfield discloses a very specific bioassay that involves IP administration of thioglycolalaste followed by the IP administration of GPI together with degalactosamine; the hyperactivation of macrophages which is designed to be induced by this assay causes host death, and where the environment is skewed one cannot assume that one would inherently induce a TH cell activation. Applicant further argues that the bioactivity in the

art reference resulted from the association of GPI with TLR4 which is a macrophage receptor and not CD1, that very little response was obtained from such administration of GPI by itself, and it was not effective. Applicant further argues that because GPI was actually bound by the TLR4 receptor of the macrophages and the macrophages were in abnormally high concentrations in the peritoneal cavity, it was likely that there would not even have been a sufficient amount of antigen to drain Peyer's Patches or other relevant lymphoid areas in order to enable stimulation of T cells to occur, and therefore the reference does not disclose each and every element of the claimed invention.

However, the art reference teaches that thioglycollate-primed mice were inoculated intraperitoneally with purified malarial GPI in saline, and showed a transient drop in blood glucose concentration and signs of a transient pyrexia, but did not die as a result of this treatment. Applicant is correct in stating that the purified GPI administered in this was manner not effective, however Applicant does not mention that the way in which the GPI was not effective was in not inducing death of the mice. Administration of GPI appears to mimic some of the effects of infection without killing the mice. The art reference teaches that the sensitivity of the mice to the lethal effects of TNF may be markedly increased by exposure to a variety of bacterial agents, or to D-galactosamine. Applicant does not present evidence [of GPI binding to TLR4R on macrophages or] that GPI will be sufficiently depleted or not presented by APC such as macrophages to recruit or stimulate T cells. The art reference teaches administration of GPI by itself, said administration not resulting in death of the animals, said teaching meeting the instant claim limitations as enunciated supra. The Examiner points out that the method of the instant claims recites "comprising" as the open transitional language, indicating that other steps may be present.

Furthermore, several of the cited evidentiary references teach that CD1d binds GPI and stimulates NK T cells. Schofield *et al* (1999) further teach that the proliferative and IL-4 (*i.e.,* Th2 cytokine) response to PfGPI of NK 1.1+/CD4+ T cells is independent of MHC and can be blocked by an anti-CD1 mAb, indicating CD1 restriction. The said Schofield evidentiary reference teaches that CD4+ NKT cells are stimulated by GPIs in a CD1d-dependent manner and that such recognition is mediated by the glycan moiety, administration of GPIs being either *in vitro* or *in vivo*.

Therefore, it is the Examiner's position that the art reference inherently teaches activation of Th cells following administration of GPI.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 stand rejected under 35 U.S.C. 103(a) as being obvious over WO 99/52547 (10/21/99, of record) in view of Gerold *et al* (J. Biol. Chem. 1994 269(4): 2597-2606, of record) and Gerold *et al* (Mol. Biochem. Parasit. 1996 75: 131-143, of record).

WO 99/52547 teaches treatment of malaria or other parasitic infections comprising administering CD1-binding GPI to induce a $CD4^+$ T cell response, including inducing B cell activation through a T cell response, *i.e.,* activation of $CD4^+$ Th2 cells (especially page 3 at lines 9-21, pages 9-10, 12, 18, 19 and claims). WO 99/52547 teaches *Plasmodium* genus and species (especially pages 3, 10, 11 and 12 and claims). WO 99/52547 further teaches phospholipids such as phosphatidylinositol, phosphatidylethanolamine and phosphatidylglycerol (page 21). WO 99/52547 teaches that the immunogenic composition for treating malaria can comprise a CD1-restricted lipid antigen from *Plasmodium*, such as a GPI (especially page 11 and claims).

WO 99/52547 does not teach the treatment of malaria or other parasitic infections comprising a GPI that comprises the structure recited in the instant claims.

Gerold *et al* (1994) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane. Gerold *et al* (1994) teach that MSP-1 and MSP-2 possess GPI anchors with the same neutral glycan as $Pf_{g1}\alpha$. Gerold *et al* (1994) teach that they are supposed to have the structure ethanolamine-phosphate-Mα2Mα2Mα6Mα4GlcN-PI based upon identical fragmentation products to the *T. brucei* GPI-anchor precursor P2, and the said structure further comprises a lipid (see entire article). Gerold *et al* (1994) teach that elucidation of the structures of malarial GPIs may provide a basis for the development of a glycolipid-based vaccine for malaria (page 2605, column 2, second to last paragraph).

Gerold *et al* (1996) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane, the GPI anchors having the Mα2Mα2Mα6Mα4-GlcInositol phosphate linked to diacyl glycerol, a lipid. Gerold *et al* (1996) also teach that the core glycans of both protein-GPI anchors possess the same structure as the potential GPI-anchor precursor $Pf_{g1}\alpha$ taught by the Gerold *et al* (1994) cited below. Gerold *et al* (1996) teach that antibodies to malarial GPIs are able to block cytokine induction by whole parasite extracts, that the said GPIs are the major toxin of malarial origin and that they play a central role in the etiology of clinical severe and cerebral malaria (see entire article).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the malarial GPI taught by either Gerold *et al* reference as the GPI taught by WO 99/52547 in the method taught by WO 99/52547.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat malaria because WO 99/52547 teaches treating malaria by administering CD1-binding GPI to induce a $CD4^+$ T cell response, and the Gerold *et al* references teach the structure of the MSP-1 and MSP-2 GPIs from malaria that are taught by the said references to provide a basis for vaccines and that play a central role in the etiology of clinical severe and cerebral malaria.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. When a claim recites using an old composition or structure (*e.g.,* GPI or analogues) and the use is directed to a result or property of that composition or structure (activating $CD4^+$ $NK1.1^+$ Th2 cells following administration of GPI) then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. v. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. v IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Applicant's arguments of record in the amendment filed 9/11/08 on pages 10-11 have been fully considered, but are not persuasive.

Applicant has argued that the subject matter taught in the primary reference is found in Applicant's priority document filed before the publication of the said primary reference, and therefore, Applicant has effectively antedated the said reference and has disqualified it as prior art, as supported by the legal principal established in In re Stemple, 241 F2d 755, 760 (CCPA 1957) (that a reference is valid only for what it discloses and if Applicants establish priority with respect to such disclosure, the reference is of no effect at all…the priority document only needs to disclose as much as the primary reference.)

However, In re Stemple is not relevant to the instant situation. The question in In re Stemple was "When a domestic patent discloses only a single species of an invention and the Applicant submits an affidavit under Rule 131 showing completion of the invention of that species prior to the effective date of the reference (which does not claim it), can that reference be used as the basis of the rejection of generic claims in the application?" In re Stemple does not pertain to a 103(a) rejection, but rather to a 102 rejection, and nowhere does it determine that a priority document only needs to disclose as much as the primary reference.

11. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 stand rejected under 35 U.S.C. 103(a) as being obvious over WO 99/52547 (10/21/99, of record) in view of Schofield *et al* (J. Exp. Med. 1/93 177: 145-153, of record).

WO 99/52547 teaches treatment of malaria or other parasitic infections comprising administering CD1-binding GPI to induce a $CD4^+$ T cell response, including also inducing B cell activation through a T cell response, *i.e.,* activation of $CD4^+$ Th2 cells (especially page 3 at lines 9-21, pages 9-10, 12, 18, 19 and claims). WO 99/52547 teaches *Plasmodium* genus and species (especially pages 3, 10, 11 and 12 and claims). WO 99/52547 further teaches phospholipids such as phosphatidylinositol, phosphatidylethanolamine and phosphatidylglycerol (page 21). WO 99/52547 teaches that the immunogenic composition for treating malaria can comprise a CD1-restricted lipid antigen from *Plasmodium*, such as a GPI (especially page 11 and claims).

WO 99/52547 does not teach the treatment of malaria or other parasitic infections comprising a GPI that comprises the structure recited in the instant claims.

Schofield *et al* teach a strong correlation between TNF and IL-1 levels in sera of malarious individuals and the severity of the disease, wherein plasma TNF levels were twice as high in surviving cerebral malaria patients as in those with uncomplicated malaria, and those that died of the cerebral malarial disease had ten times elevated levels. Schofield *et al* teach that administration *in vivo* of specific neutralizing antibodies against TNF affords some protection to mice infected with lethal malaria. Schofield *et al* teach that excess production of TNF in response to the malarial parasite contributes to the severe pathology and death in both rodent and human infections. Schofield *et al* teach administration *in vivo* in mice of P. *falciparum* or T. *brucei* GPI or analogues that also comprise diacylglycerol and phosphatidylcholine. Schofield *et al* teach that several major antigens of the malaria parasite are covalently linked to GPI, including the MSP-1 and MSP-2 antigens on the merozoite surface, currently under consideration as vaccine candidates. Schofield *et al* teach that immunization of mice with highly purified malaria GPI prepared from mature P. *falciparum* MSP-2 leads to a serological anti-GPI response with T independent features, and the anti-GPI sera are able even at high titration to neutralize TNF induction and lipogenesis by both the heterologous MSP-1 antigen and whole parasite extracts, *i.e.,* anti-GPI administered for treatment of induced malarial disease *in vivo* in mice. Schofield *et al* teach providing clinical protection against malarial disease, either by passive transfer of neutralizing anti-GPI antibodies or by immunization against the GPI or various non-toxic analogues for *in vivo* production of anti-GPI antibodies (especially page 152, page 149, page 150). Schofield *et al* teach cerebral malaria is a type of malaria to be treated by administering GPI (see entire article, especially introduction on pages 145-146, page 146 at the third full paragraph, results and discussion, page 152 at column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the P. *falciparum* GPI taught by Schofield *et al* as the GPI in the method taught by WO 99/52547.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat malaria because WO 99/52547 teaches treating malaria by administering CD1-binding GPI to induce a $CD4^+$ T cell response, and Schofield *et al* teach the structure of a P. *falciparum* GPI that is linked to the MSP-1 and MSP-2 antigens on the malarial merozoite surface that are under consideration as vaccine candidates, that immunization of mice with highly purified malaria GPI prepared from mature P. *falciparum* MSP-2 leads to a serological anti-GPI response with T independent features, and that the anti-GPI sera are able even at high titration to neutralize TNF induction and lipogenesis by both the heterologous MSP-1 antigen and whole parasite extracts.

Applicant's arguments of record in the amendment filed 9/11/08 on pages 10-11 have been fully considered, but are not persuasive.

Applicant has argued that the subject matter taught in the primary reference is found in Applicant's priority document filed before the publication of the said primary reference, and therefore, Applicant has effectively antedated the said reference and has disqualified it as prior art, as supported by the legal principal established in In re Stemple, 241 F2d 755, 760 (CCPA 1957) (that a reference is valid only for what it discloses and if Applicants establish priority with respect to such disclosure, the reference is of no effect at all…the priority document only needs to disclose as much as the primary reference.)

However, In re Stemple is not relevant to the instant situation. The question in In re Stemple was "When a domestic patent discloses only a single species of an invention and the Applicant submits an affidavit under Rule 131 showing completion of the invention of that species prior to the effective date of the reference (which does not claim it), can that reference be used as the basis of the rejection of generic claims in the application?" In re Stemple does not pertain to a 103(a) rejection, but rather to a 102 rejection, and nowhere does it determine that a priority document only needs to disclose as much as the primary reference.

12. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 stand rejected under 35 U.S.C. 103(a) as being obvious over WO 99/12562 A1 (3/18/99, of record) in view of Gerold *et al* (J. Biol. Chem. 1994 269(4): 2597-2606, of record) and Gerold *et al* (Mol. Biochem. Parasit. 1996 75: 131-143, of record).

WO 99/12562 A1 teaches treatment parasitic infections in a mammal, including malaria, comprising administering a CD1-restricted antigen such as a GPI that comprises a hydrophilic component conjugated to a hydrophobic component that comprises one or

more saturated or unsaturated acyl chains and wherein one or more of the acyl chains is bonded to a phosphate group. WO 99/12562 A1 teaches that glycosyl phosphatidylinositols (GPIs) have two alkyl chains and a hydrophilic head group that conform to the CD1d motif and are presented by CD1d in both humans and mice (especially abstract, page 3 at lines 8-15, page 16 at lines 25-30, page 28 at lines 15-33, page 29 at lines1-10, claims 10-17).
WO 99/12562 A1 does not teach the treatment of malaria or other parasitic infections comprising a GPI that comprises the structure recited in the instant claims.

Gerold *et al* (1994) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane. Gerold *et al* (1994) teach that MSP-1 and MSP-2 possess GPI anchors with the same neutral glycan as $Pf_{g1}\alpha$. Gerold *et al* (1994) teach that they are supposed to have the structure ethanolamine-phosphate-Mα2Mα2Mα6Mα4GlcN-PI based upon identical fragmentation products to the *T. brucei* GPI-anchor precursor P2, and the said structure further comprises a lipid (see entire article). Gerold *et al* (1994) teach that elucidation of the structures of malarial GPIs may provide a basis for the development of a glycolipid-based vaccine for malaria (page 2605, column 2, second to last paragraph).

Gerold *et al* (1996) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane, the GPI anchors having the Mα2Mα2Mα6Mα4-GlcInositol phosphate linked to diacyl glycerol, a lipid. Gerold *et al* (1996) also teach that the core glycans of both protein-GPI anchors possess the same structure as the potential GPI-anchor precursor $Pf_{g1}\alpha$ taught by the Gerold *et al* (1994) cited below. Gerold *et al* (1996) teach that antibodies to malarial GPIs are able to block cytokine induction by whole parasite extracts, that the said GPIs are the major toxin of malarial origin and that they play a central role in the etiology of clinical severe and cerebral malaria (see entire article).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the malarial GPI taught by either Gerold *et al* reference as the GPI taught by WO 99/12562 A1 in the method taught by WO 99/12562 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat malaria because WO 99/12562 A1 teaches treating malaria by administering CD1-binding GPI to induce a T cell response and treat malaria, and the Gerold *et al* references teach the structure of the MSP-1 and MSP-2 GPIs from malaria that are taught by the said references to provide a basis for vaccines and that play a central role in the etiology of clinical severe and cerebral malaria.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. When a claim recites using an old composition or structure (*e.g.,* GPI or analogues) and the use is directed to a result or property of that

composition or structure (activating $CD4^+$ $NK1.1^+$ Th2 cells following administration of GPI) then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. v. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. v IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Applicant's arguments of record in the amendment filed 9/11/08 on pages 10-11 have been fully considered, but are not persuasive.

Applicant has argued that the subject matter taught in the primary reference is found in Applicant's priority document filed before the publication of the said primary reference, and therefore, Applicant has effectively antedated the said reference and has disqualified it as prior art, as supported by the legal principal established in In re Stemple, 241 F2d 755, 760 (CCPA 1957) (that a reference is valid only for what it discloses and if Applicants establish priority with respect to such disclosure, the reference is of no effect at all…the priority document only needs to disclose as much as the primary reference.)

However, In re Stemple is not relevant to the instant situation. The question in In re Stemple was "When a domestic patent discloses only a single species of an invention and the Applicant submits an affidavit under Rule 131 showing completion of the invention of that species prior to the effective date of the reference (which does not claim it), can that reference be used as the basis of the rejection of generic claims in the application?" In re Stemple does not pertain to a 103(a) rejection, but rather to a 102 rejection, and nowhere does it determine that a priority document only needs to disclose as much as the primary reference.

13. Claims 1-3, 9-16, 18, 81-88, 100, 102-106, 108-110, 116-120, 124 and 125 stand rejected under 35 U.S.C. 103(a) as being obvious over WO 99/12562 A1 (3/18/99, of record) in view of Schofield *et al* (J. Exp. Med. 1/93 177: 145-153, of record).

WO 99/12562 A1 teaches treatment parasitic infections in a mammal, including malaria, comprising administering a CD1-restricted antigen such as a GPI that comprises a hydrophilic component conjugated to a hydrophobic component that comprises one or more saturated or unsaturated acyl chains and wherein one or more of the acyl chains is bonded to a phosphate group. WO 99/12562 A1 teaches that glycosyl phosphatidylinositols (GPIs) have two alkyl chains and a hydrophilic head group that conform to the CD1d motif and are presented by CD1d in both humans and mice (especially abstract, page 3 at lines 8-15, page 16 at lines 25-30, page 28 at lines 15-33, page 29 at lines1-10, claims 10-17).

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Schofield *et al* teach a strong correlation between TNF and IL-1 levels in sera of malarious individuals and the severity of the disease, wherein plasma TNF levels were twice as high in surviving cerebral malaria patients as in those with uncomplicated malaria, and those that died of the cerebral malarial disease had ten times elevated levels. Schofield *et al* teach that administration *in vivo* of specific neutralizing antibodies against TNF affords some protection to mice infected with lethal malaria. Schofield *et al* teach that excess production of TNF in response to the malarial parasite contributes to the severe pathology and death in both rodent and human infections. Schofield *et al* teach administration *in vivo* in mice of P. *falciparum* or T. *brucei* GPI or analogues that also comprise diacylglycerol and phosphatidylcholine. Schofield *et al* teach that several major antigens of the malaria parasite are covalently linked to GPI, including the MSP-1 and MSP-2 antigens on the merozoite surface, currently under consideration as vaccine candidates. Schofield *et al* teach that immunization of mice with highly purified malaria GPI prepared from mature P. *falciparum* MSP-2 leads to a serological anti-GPI response with T independent features, and the anti-GPI sera are able even at high titration to neutralize TNF induction and lipogenesis by both the heterologous MSP-1 antigen and whole parasite extracts, *i.e.,* anti-GPI administered for treatment of induced malarial disease *in vivo* in mice. Schofield *et al* teach providing clinical protection against malarial disease, either by passive transfer of neutralizing anti-GPI antibodies or by immunization against the GPI or various non-toxic analogues for *in vivo* production of anti-GPI antibodies (especially page 152, page 149, page 150). Schofield *et al* teach cerebral malaria is a type of malaria to be treated by administering GPI (see entire article, especially introduction on pages 145-146, page 146 at the third full paragraph, results and discussion, page 152 at column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the P. *falciparum* GPI taught by Schofield *et al* as the GPI in the method taught by WO 99/12562 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat malaria because WO 99/12562 A1 teaches treating malaria by administering CD1-binding GPI to induce a T cell response, and Schofield *et al* teach the structure of a P. *falciparum* GPI that is linked to the MSP-1 and MSP-2 antigens on the malarial merozoite surface that are under consideration as vaccine candidates, that immunization of mice with highly purified malaria GPI prepared from mature P. *falciparum* MSP-2 leads to a serological anti-GPI response with T independent features, and that the anti-GPI sera are able even at high titration to neutralize TNF induction and lipogenesis by both the heterologous MSP-1 antigen and whole parasite extracts.

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However, In re Stemple is not relevant to the instant situation. The question in In re Stemple was "When a domestic patent discloses only a single species of an invention and the Applicant submits an affidavit under Rule 131 showing completion of the invention of that species prior to the effective date of the reference (which does not claim it), can that reference be used as the basis of the rejection of generic claims in the application?" In re Stemple does not pertain to a 103(a) rejection, but rather to a 102 rejection, and nowhere does it determine that a priority document only needs to disclose as much as the primary reference.

14. Claims 1-3, 9-12, 14-16, 18, 81-87, 100 and 102 stand rejected under 35 U.S.C. 103(a) as being obvious over WO 96/34105 A1 (IDS reference submitted 6/11/07) as evidenced by Gerold *et al* (Mol. Biochem. Parasit. 1996 75: 131-143, of record), Gerold *et al* (J. Biol. Chem. 1994 269(4): 2597-2606, of record) and Joyce *et al* (Science 1998 279: 1541-1543, IDS reference).

WO 96/34105 A1 teaches producing antibodies (*i.e.,* activating Th cell help for antibody production) by administering a complex of GPI-antigen, the antigen such as a parasite polypeptide, in particular, a *P. falciparum* polypeptide (see entire reference, especially abstract, page 3 at lines 4-15, page 12, page 13 at lines 1-15, claims).

WO 96/34105 A1 does not teach the structure of the GPI used in the method.

Gerold *et al* (1996) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane, the GPI anchors having the Mα2Mα2Mα6Mα4-GlcInositol phosphate linked to diacyl glycerol, a lipid. Gerold *et al* (1996) also teach that the core glycans of both protein-GPI anchors possess the same structure as the potential GPI-anchor precursor $Pf_{g1}\alpha$ taught by the evidentiary reference Gerold *et al* (1994) cited below (see entire article).

Gerold *et al* (1994) teach that the MSP-1 and MSP-2 merozoite surface proteins of *Plasmodium falciparum* isolate FCBR are anchored via GPI to the membrane. Gerold *et al* (1994) teach that MSP-1 and MSP-2 possess GPI anchors with the same neutral glycan as $Pf_{g1}\alpha$. Gerold *et al* (1994) teach that they are supposed to have the structure ethanolamine-phosphate-Mα2Mα2Mα6Mα4GlcN-PI based upon identical fragmentation

products to the *T. brucei* GPI-anchor precursor P2, and the said structure further comprises a lipid (see entire article).

Joyce *et al* teach that CD1d binds GPI through its phosphatidylinositol aspect with high affinity. Joyce *et al* further teach that CD1d controls the function of NK1+ T cells that play an immunoregulatory role in responses to foreign and self antigens.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the GPI from *P. falciparum* taught by Gerold *et al* (1996) and Gerold *et al* (1994), that is taught by Joyce *et al* to bind CD1d, as the GPI in the complex comprising GPI and a *P. falciparum* polypeptide antigen taught by WO 96/34105 A1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 96/34105 A1 teaches a GPI-peptide complex for immunizing animals and producing antibodies wherein the peptide is from *P. falciparum*, Gerold *et al* (1996) and Gerold *et al* (1994) teach the structure of GPI from *P. falciparum*, and Joyce et al teach that CD1d binds GPI through its phosphatidylinositol aspect with high affinity. Joyce *et al* further teach that CD1d controls the function of NK1+ T cells that play an immunoregulatory role in responses to foreign and self antigens.

Claims 16 and 83 are included in this rejection because it is an expected property of the NK1+ T cells taught by Joyce *et al* that they are CD4+ T cells.

Claims 81-87 are included in this rejection because GPI is administered even though it is present in a complex.

Claim 102 is included in this rejection because it is an expected property of the art method that the activated T cells induce or up-regulate a TH2 type response.

Applicant's arguments in the response filed 9/11/08 have been fully considered, but are not persuasive.

Applicant's said arguments are of record on pages 11-12 of the said response, briefly that the disclosure teaches the activation of Th cells. Applicant argues that it is commonly known that although Th cells are often required for B cell responsiveness to a protein antigen, T-independent antibody responses commonly occur to microbial agents such as bacterial polysaccharides, and accordingly, one cannot make the assumption that the GPI molecule which has been attached to the protein in the prior art reference is in fact functioning via a T cell dependent mechanism. Applicant argues that it is generally understood that there are certain properties of some bacterial polysaccharides, polymeric proteins and lipid polysaccharides that enable stimulation of naive B cells in the absence of T cell help.

However, Joyce *et al* teach that CD1d binds GPI through its phosphatidylinositol aspect with high affinity. Joyce *et al* further teach that CD1d controls the function of NK1+ T cells that play an immunoregulatory role in responses to foreign and self antigens, and it is an expected property of the said NK1+ T cells that they are CD4+T cells that provide help. Applicant has not provided evidence that GPI is a T independent antigen. Motivation exists for combining the references, and it is the Examiner's position that such combination would have produced the claimed invention with a reasonable expectation of success.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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November 28, 2008

/Michael Szperka/
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